solid-phase binding assay. Support for purifying the recited NHR receptor is found on p.3, line 20; support for the binding assay is found in Example II. These amendments introduce no new matter.

35USC112, first paragraph - written description

The claims are in compliance with 35USC112, first paragraph (written description). The Action restates the appealed-from rejection and we rely on the remarks set forth in our Brief on Appeal. The Action's new reliance on Montminy (1997 Nature 387:654-55) and Heery et al. (1997 Nature 387:733-36) is misplaced, as these references do not disclose or suggest the claimed assays and all peptides which failed to work in their studies do not fail to work in our assays.

35USC112, first paragraph - enablement

The claims are in compliance with 35USC112, first paragraph (enablement). The Action restates the appealed-from rejection and we rely on the remarks set forth in our Brief on Appeal. The Action's new reliance on orphan receptors (citing Mangelsdorf et al. 1995 Cell 83:841-50) is misplaced, because the Action presumes the claims require a natural ligand for the recited receptor. This is not true. In fact, the assay is commercially used primarily with orphan receptors, wherein a "natural" ligand is not even known. Orphan NHRs provide uniquely easily targeted, specific handles for regulating gene expression and physiological function and they are routinely exploited as commercial drug targets without knowledge of their "natural" ligand(s), binding site(s) or particular function (37CFR1.132 Declaration, attached). In fact, orphan receptors provide some of the "hottest" present receptor targets in the pharmaceutical industry (see, e.g. Blumberg et al., 1998, Genes & Dev 12, 1269-77; Dussault et al., 2001, J Biol Chem 276, 33309-33312; Enmark and Gustafsson (1996) Mol Endocrinol 10:1293-1306, all enclosed). Finally, we note that the Action's remarks on p.4, lines 9-23 are directed to claims 18-20 and 23-37, which are not found in this application, but are found in copending 08/975,614.

35USC112, second paragraph

The phrases "agent-biased binding" and "unbiased binding" are clear in their context as 'binding

biased by the presence of the agent', and 'binding not biased by the presence of the agent'; see also, Specification, p.8, lines 3-11: "The mixture is incubated under conditions whereby, but for the presence of the candidate agent, the sensor binds the receptor with a reference binding affinity.... After incubation, the agent-biased binding between the sensor and receptor is detected according to the nature of the label, as described above. A difference in the binding in the presence and absence of the agent indicates that the agent modulates a receptor binding function."

The recited "measuring step" has antecedent basis in the measuring step of the parent claim (canceled claim 32); note that the method comprises "steps" and one of the recited steps is a "measuring" step.

35USC102(a) and 35USC103(a)

The claims are restricted to an in vitro solid-phase binding assay that requires direct, ligand-dependent sensor peptide binding to a nuclear hormone receptor. Such an assay was not only not suggested by the cited art, but that such an assay could be devised was entirely unexpected from the cited art.

The claims are restricted to an in vitro fluorescence polarization assay that requires direct, ligand-dependent and highly specific (nanomolar affinity) sensor peptide binding to a nuclear hormone receptor. Such an assay was not only not suggested by the cited art, but that such an assay could be devised was entirely unexpected from the cited art.

The cited Heery et al. (1997, Nature 387,733-36)[1] describes three experiments: the first is an in vivo yeast-based two-hybrid experiment wherein a DNA-binding domain fusion protein comprising LXXLL motifs activated transcription through a ligand-binding domain of an estrogen receptor (Fig.1). The second experiment is a GST pull-down experiment wherein GST-ER fusion proteins pulled down in vitro translated ^{35}S-labeled natural-sequence SRC-1 proteins, but not otherwise identical mutant-sequence SRC-1 proteins wherein all four functional LXXLL motifs were disabled (Fig.3a). In this

[1] We do not agree with the Action's proposed construction of our claims; for example, Heery's use of a natural SRC-1 coactivator protein is not encompassed by our recited mixture, which precludes the presence of a natural coactivator protein. A natural SRC-1 coactivator protein is a natural coactivator protein regardless of how it is made.

experiment, the natural sequence SRC-1 pull-down was inhibited by uM concentrations of LXXLL peptides (Fig.3b). The third experiment showed that natural SRC-1 but not mutant SRC-1 increased activation of estrogen receptor in HeLa cells transiently transfected with a reporter plasmid (Fig.3c).

One skilled in the art would not construe Heery to suggest the feasibility of assaying direct, in vitro LXXLL peptide to purified receptor; in fact, to one skilled in the art, Heery suggests the opposite - that such an assay would not be feasible. First, Heery provides no data suggesting an LXXLL peptide can directly bind the receptor. Heery's two-hybrid transcriptional activation is performed within yeast cells, the GST pull-down assay is performed in a crude cellular lysate[2], and the third, transient transfection experiment is cell-based. One skilled in the art would recognize that all of these experiments report both higher and lower order complex formation and that none of them implies direct peptide-receptor binding.

Similarly, none of Heery's data imply that an LXXLL peptide is sufficient to bind the receptor; in fact, they suggest the opposite. For example, one skilled in the art would recognize that Heery does not report any GST pull-down of an LXXLL peptide, nor any data wherein a single LXXLL motif was disrupted, but only wherein all four were disrupted. In fact, one skilled in the art would conclude that the author's failure to provide such data suggests that single LXXLL-motif disruptions may not have worked. In fact, this negative inference is further compelled by the subsequent inhibition experiments, wherein the authors only report data wherein uM concentrations of peptide were required to inhibit pull down - orders of magnitude higher than the amount of the SRC-1 protein present (the disclosed in vitro transcriptional yield is on the order of a few nM). One skilled in the art would conclude that the disproportionately high concentration of peptide necessary to inhibit SRC-1 pull-down suggests that LXXLL peptides do not provide sufficient receptor binding affinity to permit a direct, binding assay.

In short, none of Heery's data suggest that the single peptides would be able to directly bind purified receptor proteins. Viewed through the eyes of one skilled in the art, Heery teaches away from an assay that relies on direct, in vitro, ligand-dependent LXXLL peptide binding to purified receptor. The secondary references do not and can not reverse Heery's contrary teachings. In particular, the

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[2] Heery cites L'Horset et al. (1996, Mol Cell Biol 16, 6029-6036, enclosed) for GST pull-down assay details, including the reticulocyte lysates.

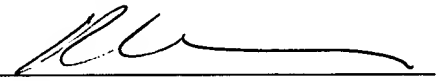
cited disclosures of eptitope tags (Torchia) fluorescent tags (Pantoliano) and FRET-bases assays (Mathis) do not and can not overcome Heery's teaching away from direct, in vitro LXXLL peptide - receptor binding.

To expedite prosecution, we provide herewith evidence in the form of an expert Declaration averring the foregoing. Accordingly, the uncontroverted evidence of record demonstrates that the claimed invention was not obvious to one skilled in the art in view of the cited art.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

Appellants hereby petition for and authorize charging to our Deposit Account No. 19-0750 all necessary extensions of time. The Commissioner is hereby authorized to charge any necessary fees or credit any overpayments associated with this communication to our Deposit Account No. 19-0750 (order no. T97-012-1).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



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enc. 37CFR1.132 Declaration from parent 08/975,614 (2p).
Blumberg et al., 1998, Genes & Dev 12, 1269-77 (9 p.)
Dussault et al., 2001, J Biol Chem 276, 33309-33312 (4 p.)
Enmark and Gustafsson (1996) Mol Endocrinol 10:1293-1306 (14 p.)
L'Horset et al. (1996) Mol Cell Biol 16, 6029-6036 (7 p.)